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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/939,884 | 08/27/2001 | Ray Yin | DAM 563-01 | 5229 |

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US ARMY SOLDIER AND BIOLOGICAL CHEMICAL COMMAND
OFFICE OF THE CHIEF COUNSEL/IP TEAM (BLDG E4435)
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| EXAMINER | |
|---|---|
| DO, PENSEE T | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1641 | |

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/939,884 | YIN ET AL. | |
| | Examiner | Art Unit | |
| | Pensee T. Do | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The present specification lacks description for a third-generation (G3, ***PA32***) and fourth generation (G4, ***PA64***) polypropyleneimine dendrimer.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

*The nature of the invention:* - the instant invention is directed to a composition comprising a molecularly compact polymer-ligand conjugate capable of self-orienting on a surface wherein said molecularly compact polymer comprises a generation 1 (G1) to

10 (G10) polyamidoamine dendrimer having surface functional groups, wherein said surface functional groups comprise about 75% hydroxyl groups and about 25% primary amine groups and the ligand is bound to molecular compact polymer and said compact polymer binds to said surface such that the ligand is uniformly positioned opposite to said surface.

*The state of the art*: - the prior art teaches the compact polymer comprises a generation 1-10 but fails to teach a compact polymer comprises the specific generation 3 (G3, PA32) and generation 4 (G4, PA64) dendrimer.

*The predictability or lack thereof in the art:*- in view of the lack of teachings in the prior art that show or suggests generation 3 (G3, PA32) and generation 4 (G4, PA64) dendrimer, the predictability of one of ordinary skills in the art is high.

*The amount of direction or guidance present:* - the instant specification fails to provide guidance on how to generate G3, PA32 and G4, PA64 dendrimer.

*The presence or absence of working examples*:- there is no examples in the specification that show how to generate G3, PA32 and G4, PA64.

*The quantity of experimentation necessary:* - it would require an undue amount of experimentation for a skilled artisan to make and use the invention as claimed.

*The relative skill of those in the art*: The level of skill in the art is high.

*The breadth of the claims*:- the claimed composition is directed to a molecularly compact polymer-ligand conjugate.

The specification fails to describe or show examples of how to generate G3, PA32 and G4, PA64 dendrimers.

***Claim Rejections - 35 U.S.C. ' 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 3718 of this title before the invention thereof by the applicant for patent.

Claims 1, 9, 13, 21, 25, 33, 37, 45, 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by Tomalia et al. (US Patent 5,338,532).

Tomalia et al. teach STARBURST or polyamidoamine conjugates (dendritic polymer) which are composed of at least one dendrimer in association with at least one unit of a carried agricultural, pharmaceutical, or biological materials. The starburst dendrimers are unimolecular assemblages that possess three distinguish architectural features, namely, (a) an initiator core, (b) interior layers (generations, G) composed of repeating units, radially attached to the initiator core, and (c ) an exterior surface of terminal functionality (i.e. terminal functional groups) attached to the outermost generation. The size and shape of the starburst dendrimer molecule and the functional groups present in the dendrimer molecule can be controlled by the choice of the initiator core, the number of generations (i.e. tiers) employed in creating the dendrimer, and the choice of the repeating units employed at each generation. Since the dendrimers can be isolated at any particular generation, a means is provided for obtaining dendrimers having desired properties. Tomalia et al. also teach the method for the preparation of

Polyetheyleneimines and polyamidoamines dendrimers including the 10 generations of the dendrimers. The size in diameter of the dendrimers is ranging from 20-60 Ahmstrong (equals 2-6 nanometers). The carried pharmaceutical materials include scavenging agents such as chelants, antigens, antibodies, etc. Dendrimer surface functionalities provide useful functional groups such as hydroxyl, alkyl, etc. (See col. 24, lines 61-62). Regarding the percentage of the hydroxyl functional groups, routine experimentation can be done to accomplish such percentages of the hydroxyl functional groups. Dendritic polymers often consist of dendrimers, dendrigrafts and hyper-branched polymers.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 14, 15, 26, 27, 38, 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al. (US 5,338,532) in view of Klimash et al. (US 6,020,457).

Tomalia et al. has been discussed above.

However, Tomalia fails to teach that the ligand is selected from the group consisting of IgG molecules and Fab antibody fragments and that the surface is selected from the group consisting of immunoassay test strips, glass, nitrocellulose,

paper, quartz, plastics, colloidal particles, metals, polymer latex beads, clays, ceramics, up-converting phosphorescent particles and quantum dots.

Klimash et al. teach a method of preparing a self-assembled dendrimer monolayers on quartz crystal resonators to provide dendrimer-modified electrodes which are useful for detecting various ions or molecules. Klimash et al. also teach dendritic polymers containing disulfide functional groups which are essentially inert under non-reducing conditions, but which form sulfhydryl groups upon being subjected to a reducing agent. These dendritic polymers have a plurality of surface function groups (such as amines) which can be used for purposes of signal amplification, attachment to surfaces, analyte interaction, further conjugation, etc. The dendritic polymer can be coupled with bioactive agents such as antibodies, antibody fragments, toxins, hormones, biological responses modifiers, scavenging agents, antigens, polypeptides, pharmaceutical agents, drugs, genetic materials, etc. The dendritic polymers used to prepare different functional groups to produce differentiated dendrimers having a first type of functional groups which is isolated to a first sector or surface area of the polymer and a second type of functional group which is isolated to a second sector or surface area of the polymer. (See col. 7, lines 27-55, line 65-col. 8, line 10; col. 21, line 5-col. 22, line 60).

It would have been obvious to one of ordinary skills in the art to use quartz as the surface for binding polymer and coupling dendritic polymer to antibody fragments as taught by Klimash in the composition of Tomalia since both references teach the same basic components of the same composition. The disulfide core of the dendritic

polymers can be used in the preparation of self-assembled monolayer on a quartz crystal resonator to allow for the sensitive detection of mass buildup on the surface of the electrode. The disulfide linkage of the dendritic polymer can react with gold surface of the electrode to form a self-assembled monolayer. These dendrimer-modified electrodes can be used to detect variety of small molecules (for example, copper ions) or even larger biomolecules. (see Klimash, col. 8, lines 33-41). Furthermore, it is an advantage for using antibody fragments as specific receptor/ligand for assaying many different specific analytes.

Claims 3-6, 15-18, 27-30, 39-42, 49, 54-57, rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter et al. (US 5,851,777).

Tomalia has been discussed above.

However, Tomalia fails to teach the material of the surface, the colloidal particles and their size ranges.

Hunter et al. teach a method for preparing a reagent sol particle bound to ligand or ligand analogue comprising (1) conjugating the ligand/analogue to a carrier molecule selected from a first protein, dendrimer or first polymer to form a ligand conjugate; (2) binding the ligand conjugate to a sol particle to form the ligand bound sol; (3) stabilizing the ligand bound sol particle with a blocking agent selected from a second protein, a detergent, or second polymer. The solid phase component e.g. latex, glass or sepharose bead, labeled with an immunological component, which interacts with another immunological component bound to a gold colloid, to form a metal-containing

solid phase which is collected for visual inspection. The size of the sol particles ranges from 5 nm to 200 nm. (See col. 5, line 16-col. 9, line 27; col. 11, lines 13-16).

It would have been obvious to one of ordinary skills in the art to conjugate a ligand to a dendrimer to form a ligand-dendrimer conjugate as taught by Hunter according to the composition specifications taught by Tomalia because colloidal particles are well known for use as labels in assays for detecting low concentrations of analyte. The size range and composition of the sol particle will determine the wavelength at which it absorbs. The particles should have a size range up to a size that settles out of solution. Particles with the size range of 5nm to 200 nm absorbs at a wavelength between 510 and 600 nm which is visible to the unaided eye.

Claims 7, 8, 19, 20, 31, 32, 43, 44, 58, 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al. in view of Hunter and further in view of Keen (US 6,060,327).

Tomalia and Hunter have been discussed above.

However, Tomalia and Hunter fail to teach that the surface can be quantum dots which are nanometer sized inorganic particles and selected among cadmium sulfide, cadmium selenide, and zinc sulfide.

Keen teaches a sensor for sensing the presence of an analyte component without relying on redox mediators. The sensor includes (a) a plurality of conductive polymer strands each having at least a first end and a second end and each aligned in a substantially common orientation; (b) a plurality of molecular recognition headgroups having an affinity for the analyte component and being attached to the first ends of the

conductive polymer strands; and (c ) an electrode substrate attached to the conductive polymer strands at the second ends. The conductive polymers include one of the followings: macrocyclic polymers, branched polymers, dendritic polymers (e.g. starburst dendrimers) (See col. 25, lines 1-50). The recognition headgroups having the affinity for the analyte component are enzymes, antibodies, antigens, receptors, cells, porphyrins, etc. (See col. 31, lines 15-40). The substrate attached to the conductive polymer strands are semiconductor substrates composed of cadmium selenide, cadmium sulfide, zinc sulfide, etc. (See col. 15, lines 60-67).

It would have been obvious to one of ordinary skills in the art to use quantum dots selected among cadmium selenide, cadmium sulfide and zinc sulfide as surface for retaining dendrimer conjugates taught by Tomalia and Hunter so that dendrimer conjugates can be used in an electrode substrate thus the analyte can be detected using biosensor containing electrodes. Tomalia teaches STARBURST as a polymeric dendrimer and Keen teaches that STARBURST can be a conductive polymer. Thus, one of ordinary skill in the art would find it obvious to combine the two references use polymeric dendrimer such as STARBURST as a conductive polymer by attaching it to a substrate such as cadmium selenide or cadmium sulfide.

Claims 10-12, 22-24, 34-36, 46-48, 50, 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia in view of Moll, III et al. (US 6,121,056) further in view of May et al. (US 5,656,503).

Tomalia has been discussed above.

However, Tomalia fails to teach a surface comprising of compressed fibers, glass, or synthetic fibers of inert cellulose materials.

Moll, III et al. teach methods, compositions and articles of manufacture for conducting specific binding assays to determine the concentration or presence of at least one analyte in a sample. At least one or two dendrimer-reagent preparations with different analyte specificities are immobilized on a solid phase. Immobilization is facilitated by coupling specific binding assay reagents such as polypeptide receptors or analytes with water soluble polymers such as star polymers such as dendrimers, which provide production advantages of lot-to-lot uniformity and homogeneity and can enhance sensitivity due to low non-specific binding to the solid phase. The solid phase is composed of a mat of compressed fibers, such as glass or synthetic fibers of relatively inert cellulose materials. The surfaces of glass fibers carry a net negative charge, which facilitates adsorption of dendrimers having substantially positively charged surfaces under assay conditions, i.e. dendrimers with amine terminal surface groups. The receptors that are coupled with the dendrimers are enzymes, antibodies, antibody fragments, etc. (See col. 5, lines 51-col. 9, line 50).

It would have been obvious to one of ordinary skills in the art to use the surface materials as taught by Moll, III in the composition of Tomalia because those materials are well known solid phase surfaces for use in solid phase assays which provide lot-to-lot uniformity to enhance the sensitivity of the assay.

However, both Tomalia and Moll, III fail to teach a composition wherein the molecularly compact polymer receptor conjugate is used on a lateral flow immunoassay strip which has a membrane surface, a conjugate release pad and an absorbent pad.

May et al. teach an analytical test device comprising a hollow casing constructed of moisture impervious solid material containing a dry porous carrier such as nitrocellulose strip which communicates directly or indirectly with the exterior of the casing such that a liquid test sample can be applied to the porous carrier, the device also contains a labeled specific biding reagent for an analyte, said labeled specific biding reagent is freely mobile within the porous carrier when in moist state, and unlabeled reagent (second antibody or capture antibody) is permanently immobilized in a detection zone on the carrier material and is therefore not mobile in the moist state, the relative positioning of the labeled reagent and detection zone being such that liquid sample applied to the device can pick up labeled reagent and thereafter permeate into the detection zone, and the device incorporating means enabling the extent to which the labeled reagent becomes in the detection zone to be observed. The device can be used in a sandwich or competition assays to determine a wide of variety of analytes such as proteins, haptens, immunoglobulins, hormones, polynucleotides, steroids, drugs, infectious disease agents (e.g. of bacterial ). May et al. also teach that the porous solid phase material comprising nitrocellulose. (See also col. 2, lines 3-45; col. 3, lines 8-12, lines 22-32; col. 6, lines 10-15; col. 9, lines 13-25; col. 15, line 56-col. 16 line 70; col. 18, line 50-col. 19, line 20).

Therefore it would have been obvious to one of ordinary skill in the art to use STARBURST dendrimers to immobilize specific biding reagent (antibodies) to a solid phase, as taught by Tomalia and Moll, III in the device of May et al. because both Tomalia & Moll, III and May et al. suggest a substrate made of cellulose and also because star dendrimers provide production advantages of lot-to-lot uniformity and homogeneity and can enhance sensitivity due to non-specific binding to the solid phase. Another advantage is that since stock or commercial solutions of dendrimer conjugates retain homogeneity over substantial periods of time, it is possible for users of commercial assay instruments to prepare these solid phase reagents on site. The use of freshly prepared solid phase reagents further eliminates additional variables that may enter into distribution and commercial use of pre-prepared solid phase reagents, such as changes due to long term storage, temperature of storage and other storage variables.

***Remarks***

Claims 63-74 are free of prior arts.

The prior art fails to teach a G3, PA32 or G4 PA64 polypropyleneimine dendrimer.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 703-308-4398. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 703-305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Pensee T. Do
Patent Examiner
September 30, 2003

LONG V. LE
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10/02/03